a network of water mediated hydrogen bonds that help stabilize the RNA duplex (Egli *et al., Biochemistry*, **1996**, *35*, 8489-8494).

[0017] DNA:RNA hybrid duplexes are usually less stable than pure RNA:RNA duplexes, and depending on their sequence may be either more or less stable than DNA:DNA duplexes (Searle *et al., Nucleic Acids Res.*, **1993**, *21*, 2051-2056). The structure of a hybrid duplex is intermediate between A- and B-form geometries, which may result in poor stacking interactions (Lane *et al., Eur. J. Biochem.*, **1993**, *215*, 297-306; Fedoroff *et al., J. Mol. Biol.*, **1993**, *233*, 509-523; Gonzalez *et al., Biochemistry*, **1995**, *34*, 4969-4982; Horton *et al., J. Mol. Biol.*, **1996**, *264*, 521-533). The stability of a DNA:RNA hybrid is central to antisense therapies as the mechanism requires the binding of a modified DNA strand to a mRNA strand. To effectively inhibit the mRNA, the antisense DNA should have a very high binding affinity with the mRNA. Otherwise the desired interaction between the DNA and target mRNA strand will occur infrequently, thereby decreasing the efficacy of the antisense oligonucleotide.

[0018] One synthetic 2'-modification that imparts increased nuclease resistance and a very high binding affinity to nucleotides is the 2'-methoxyethoxy (MOE, 2'-$OCH_2CH_2OCH_3$) side chain (Baker *et al., J. Biol. Chem.*, **1997**, *272*, 11944-12000; Freier *et al., Nucleic Acids Res.*, **1997**, *25*, 4429-4443). One of the immediate advantages of the MOE substitution is the improvement in binding affinity, which is greater than many similar 2' modifications such as *O*-methyl, *O*-propyl, and *O*-aminopropyl (Freier and Altmann, *Nucleic Acids Research*, (1997) 25:4429-4443). 2'-*O*-Methoxyethyl-substituted compounds also have been shown to be antisense inhibitors of gene expression with promising features for *in vivo* use (Martin, P.,

Helv. Chim. Acta, **1995**, *78*, 486-504; Altmann *et al.*, *Chimia*, **1996**, *50*, 168-176; Altmann *et al.*, *Biochem. Soc. Trans.*, **1996**, *24*, 630-637; and Altmann *et al.*, *Nucleosides Nucleotides*, 1997, *16*, 917-926). Such compounds typically display improved RNA affinity and higher nuclease resistance relative to DNA. Chimeric oligonucleotides with 2'-*O*-methoxyethyl-ribonucleoside wings and a central DNA-phosphorothioate window also have been shown to effectively reduce the growth of tumors in animal models at low doses. MOE substituted oligonucleotides have shown outstanding promise as antisense agents in several disease states. One such MOE substituted oligonucleotide is presently being investigated in clinical trials for the treatment of CMV retinitis.

[0019] Recently Damha et. al., published two paper describing certain oligonucleotides that utilized arabino-pentofuranosyl nucleotides as building blocks (Damha et. al., *J.A.C.S.*, **1998**, *120*, 12976-12977 and Damha et. al.,*Bioconjugate Chem.*, **1999**, *10*, 299-305). The arabino-pentofuranosyl oligonucleotides, i.e., arabinonucleic acids, described by Damha et. al., utilized either arabinose or 2'-deoxy-2'-fluoro arabinose as the sugar unit of their respective nucleotides. In one of the two arabinonucleic acids described, all of the nucleotides of the nucleic acid were arabinose and in the other, all of the nucleotides were 2'-deoxy-2'-fluoro arabinose. In both of these nucleic acids, the nucleotides were joined via phosphodiester linkages. These authors were able to show that the 2'-fluoro arabino-containing oligonucleotides when bound to RNA activated cleavage of the RNA by E. *coli* and HIV-RT RNase H. The authors further noted that while the two arabinonucleic acids they described were more stable to serum and cellular nucleases than DNA they were less stable than normal phosphorothioate deoxyoligonucleotides.

[0020] Although the known modifications to oligonucleotides have contributed to the

development of oligonuclotides for various uses, including use in diagnostics, therapeutics and as research reagents, there still exists a need in the art for further oligonucleotides having enhanced hybrid binding affinity and/or increased nuclease resistance and that can take advantage of the RNase H termination mechanism.

SUMMARY OF THE INVENTION

[0021] In one aspect, the present invention is directed to oligonucleotides having multiple properties. One of these properties is the ability to form a double stranded structure with an RNA and elicit RNase H cleavage of the RNA. Further properties of the oligonucleotides include having improved binding affinity and nuclease resistance. The oligonucleotides of the invention comprise oligonucleotide formed from a plurality of nucleotides. A first portion of the nucleotides are joined together in a contiguous sequence with each nucleotide of this portion selected as a nucleotide that has B-form conformational geometry when joined in a contiguous sequence with other nucleotides. Included in this first portion of nucleotides are ribonucleotides or arabino nucleotides. The oligonucleotides include a further portion of nucleotides that are joined together in at least one contiguous sequence. Each of these further nucleotides are selected as ribonucleotides that have A-form conformational geometry when joined in a contiguous sequence.

[0022] In preferred embodiments of the invention, each of the nucleotides of the first portion of nucleotides, independently, are selected to be 2'-SCH_3 ribonucleotides, 2'-NH_2 ribonucleotides, 2'-$NH(C_1$-C_2 alkyl) ribonucleotides, 2'-$N(C_1$-C_2 alkyl)$_2$ ribonucleotides, 2'-CF_3 ribonucleotides, 2'=CH_2 ribonucleotides, 2'=CHF ribonucleotides, 2'=CF_2 ribonucleotides, 2'-CH_3 ribonucleotides,